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ANGIOEDEMA ASSOCIATED WITH DUTASTERIDE THERAPY

Angioedema is characterized by localized, transient swelling of the deeper layer of the skin or mucous membranes of the upper respiratory or gastrointestinal tract. Angioedema can be classified into allergic, drug related, hereditary, acquired, or idiopathic angioedema.[1] Various medications have been reported to be associated with angioedema, in particular angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, and estrogen.[2] We described a case of recurrent angioedema possibly related to antiandrogen therapy and review the possible underlying mechanisms.

A 69-year-old man presented with a recent history of mild, intermittent urticaria and episodic, major, nonerythematous, nonpruritic swelling of his face. The episodes lasted for several hours and antihistamines were of questionable benefit. His medical history included hypertension, hypercholesterolemia, and benign prostate hyperplasia. His medications consisted of losartan, alfuzosin, and dutasteride, an antiandrogen agent, for several months; aspirin, 81 mg, and rosuvastatin had been added 1 month before presentation. Losartan and aspirin use was discontinued after the initial episodes of swelling, but the swelling recurred at regular intervals as earlier. There were no other obvious triggers that precipitated symptoms, including food, infection, trauma, physical factors, or preceding illness. Laboratory test results that were unremarkable included complete blood cell counts, lactase dehydrogenase levels, serum protein electrophoresis, serum and urine immunoelectrophoresis, complement levels, and C1 esterase inhibitor (C1-INH) levels. The results of tests for antibodies to hepatitis B surface antigen and hepatitis C were negative. Abdominal ultrasonography revealed fatty liver. Because there was no obvious underlying autoimmune, lymphoproliferative disorder or C1-INH deficiency to explain this patient's angioedema, dutasteride treatment was then discontinued because of its possible effects on bradykinin metabolism. The episodes of swelling were significantly reduced.

Angioedema can be caused by a variety of mechanisms, including allergic (IgE-mediated) or nonallergic (non–IgE-mediated) processes; the latter can involve activation of complement, the kallikrein-kinin system, or inhibition of the cyclooxygenase pathway, resulting in increased levels of bradykinin and cysteinyl-leukotrienes, respectively.[3]

Bradykinin, a potent vasodilator, increases vascular permeability and can lead to the development of angioedema. Bradykinin and its active metabolites are believed to be the mediators responsible for the development of angioedema in both hereditary and ACE inhibitor–induced angioedema.[4,5] In classic hereditary angioedema, decreased function of C1-INH results in unrestrained activity of factor XII, leading to increased production of bradykinin, resulting in angioedema.[5] Bradykinin is also thought to be the mediator responsible for angioedema in a condition known as estrogen-dependent inherited or factor XII angioedema.[6] In this condition, there is a gain of function mutation in the factor XII protein, which results in increased production of bradykinin, particularly when high estrogen levels increase factor XII protein levels by increasing transcription via the estrogen response element in the factor XII gene. Additional contributions from genetic polymorphisms that result in lower levels of ACE and aminopeptidase P (APP) and reduced bradykinin degradation may also contribute to the phenotype in some families.[7] In ACE inhibitor–induced angioedema, bradykinin accumulates in patients with low levels of APP, an alternate bradykinin degradation pathway that would normally operate when ACE is inhibited and no longer available to break down bradykinin.[8]

Sex hormones have important effects on enzymes responsible for bradykinin production and degradation (Fig 1). High levels of estrogen are associated with increased levels of factor XII and reduced levels of C1-INH (an inhibitor of factor XII activation), resulting in increased bradykinin production. Estrogen also suppresses ACE expression and might reduce APP levels, which result in decreased bradykinin degradation. Clinically, exogenous estrogens increase the frequency and severity of attacks in patients with hereditary angioedema. In contrast, androgens increase the levels of C1-INH, APP, and ACE, resulting in decreased bradykinin accumulation,[6] and have been an important treatment to reduce frequency and severity of attacks in patients with hereditary angioedema.

Dutasteride is a potent inhibitor of 5α-reductase I and II, which convert testosterone to its active metabolite, dihydrotestosterone (DHT).[9] Dutasteride is used clinically as an antiandrogen in benign prostate hyperplasia and male androgenic alopecia. It reduces serum DHT by more than 90% after 1 year of administration.

We speculate that the antiandrogenic properties of dutasteride contributed to bradykinin accumulation and angioedema in our patient with otherwise mild intermittent urticaria, likely by both increasing bradykinin production (antiandrogens result in lower levels of C1-INH and increased levels of factor XII) and reducing bradykinin degradation (antiandrogens result in lower levels of ACE and APP).

Although aspirin and angiotensin receptor blockers have been reported to have been associated with angioedema,[2] they do not appear to have been responsible for angioedema in this patient because discontinuation of their use had no effect on the patient's episodes of symptoms.

This case highlights the importance of considering antiandrogen drugs as an underrecognized cause of angioedema in susceptible patients because of important effects of sex hormones on bradykinin formation and breakdown. Benign prostate hyperplasia is a common condition, affecting 70% of men by 70 years of age,[9] so there is a large patient population that may be prescribed these medications. This same population may also be prescribed ACE inhibitors, which would be expected to act synergistically

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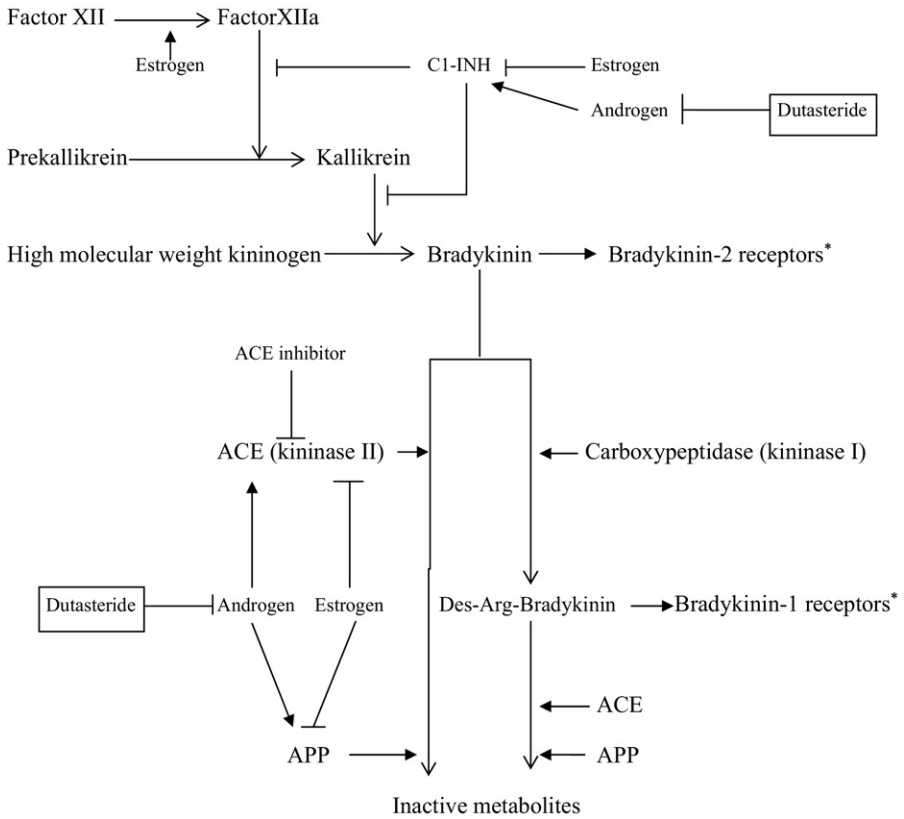

Figure 1. Bradykinin regulation pathways and interaction with sex hormones. Overall, androgens decrease bradykinin formation and increase the degradation of bradykinin and des-Arg-bradykinin, whereas estrogens have the opposite effect.[6] Steps inhibited and activated by angiotensin-converting enzyme (ACE), aminopeptidase P (APP), C1 esterase inhibitor (C1-INH), estrogen, androgen, or dutasteride are shown with *T bars* and *arrows*, respectively. *Asterisk* indicates that bradykinin and its metabolite, des-Arg-bradykinin, cause vasodilatation and increased vascular permeability, leading to angioedema.

with the antiandrogens to increase bradykinin levels and the risk of angioedema.

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FIXED DRUG ERUPTION CAUSED BY MESNA

Mesna administration usually accompanies the use of cyclophosphamide to prevent hemorrhagic cystitis. Case reports have described adverse reactions to mesna, including maculopapular rash, urticaria, and fixed drug eruption (FDE).[1,2] Among the reported cases, the appearance of FDE lesions occurred soon after the administration of mesna and before cyclophosphamide administration.[1] We report a case of FDE where the diagnosis was obscured because the lesions appeared after the completion of cyclophosphamide infusion.

A 41-year-old, African American woman, employed as a police officer at the World Trade Center site after its destruction in 2001, was diagnosed as having scleroderma and interstitial lung disease in 2004. She had an inadequate response to mycophenolate mofetil treatment in mid-2005, which was discontinued in 2007, and in 2008

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